UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,628	11/22/2004	Alberto Martin	96700/905	2223

1912 7590 11/14/2008

AMSTER, ROTHSTEIN & EBENSTEIN LLP
90 PARK AVENUE
NEW YORK, NY 10016

EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
11/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,628	MARTIN ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/21/08;2/12/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,13,15,18-25,58,97,125 and 262-307* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 13, 15, 18-25, 58, 97, 125, 262-307* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendments dated 2/12/2008 and 7/12/2008 is acknowledged. After entry of the amendments, claims 1-9, 13, 15, 18-25, 58, 97, 125, and 262-307 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

Applicant's election with traverse of the species of non-B cells in the reply filed on 7/12/2008 is acknowledged. The traversal is on the ground(s) that independent claims 1, 58, 97 and 125 all rely upon a step of expressing a transgenic AID gene in a cell, and that this step provides the special technical feature of the claims. Because all claims share this special technical feature, dependent claims directed to different cell types share this same special technical feature and thus should not be restricted. Further, applicants assert that the Examiner is incorrect in labeling the different cell types are mutually exclusive, using the example of hybridomas which are a fusion of B or T cells with myeloma cells (also a type of B cell), and thus represent overlapping subject matter if a hybridoma is to be considered both a B cell and a non-B cell.

The argument that all the independent claims possess a special technical feature is not found persuasive because as set forth in the Office Action dated 9/13/2007 and further outlined below, the independent claims do not possess a special technical feature because they are not a contribution over the prior art. However, given the extent of different cell types already examined (e.g. yeast, B cells, hybridomas) and the assertion that a hybridoma is both a B and a

non-B cell, this argument is found persuasive. The restriction requirement is withdrawn, claims 1-9, 13, 15, 18-25, 58, 97, 125, and 262-307 are pending and under examination.

Claim Rejections - 35 USC § 103

Claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US 5,885,827, of record) in view of Muramatsu et al (Cell, 2000, pp. 553-563, of record). **This rejection is maintained for reasons made of record in the Office Action dated 9/13/2007, and for reasons set forth below.**

Regarding new claims 301-303, Wabl et al teaches the selection and subcloning of cells for the desired property, e.g. a mutant μ chain, see Example 3, beginning in column 11. Also see column 8, line 41- column 9, line 5.

Regarding new claims 304-307, the hybridomas of Wabl et al are considered to be non-B cells according to applicants arguments above.

Regarding amendments to claim 13, the tet-responsive promoter in the AID vector of Muramatsu et al is at the 5' end of the AID gene, absent evidence to the contrary (as are all promoters due to the 5'-3' nature of transcription in, at the least, eukaryotes). Due to the circular nature of plasmid vectors, this promoter, along with the IRES-eGFP sequence, is considered to be at least 2000 bp of foreign sequence 5' to the AID gene for reasons set forth in the previous Office Action.

Regarding amendments to claim 97, the hybridomas taught by Wabl et al in the previous Office Action are considered to be myeloma cells in light of applicants reasoning (set forth above) that due to the nature of hybridomas being a fusion of B or T cells with a myeloma cell (also a type of B cell). Thus, if hybridomas are to be considered both a B and a non-B cell they are also considered a type of myeloma cell. Furthermore, Wabl et al teach the use of myeloma cells in, at least, Example 4. Finally, a reading of claim 307 (dependent from claim 97) reveals that hybridomas are considered a type of myeloma.

Response to Arguments

Applicant's arguments filed 2/12/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) an ordinary skilled artisan would not have an expectation of success based on the state of the art at the time of filing; 2) Wabl et al teach away from using AID in the invention, and Wabl et al do not teach expressing AID is sufficient to induce a mutator phenotype; 3) Wabl et al does not teach that the mutator cell can be fused into hybridomas; 4) Wabl et al does not teach certain limitations of the claims, such as the use of AID; 5) the IRES-EGFP of the vector used by Muramatsu et al is 3' to the AID gene; 6) the mRNA levels characterized by the Examiner as not critical to the invention are indeed critical; 7) the Examiner has not provide evidence that the truth of applicants assertions in the specification; 8) Muramatsu et al do not teach the somatic hypermutation is caused by expression of AID; 9) Muramatsu propose that AID acts as an RNA editing enzyme, and that it is not responsible for hypermutation, nor would it lead to productive stable inherited changes at the DNA level; 10) review articles (Kinoshita et al 2001, Papavasiliou et al 2002) reveal that the speculated

mechanism for AID-induced hypermutation involves RNA editing, and that this teaches away from using AID in the instant methods.

Regarding 1), such conclusory statements are not convincing in light of the highly developed state of the art presented in the published references relied upon.

Regarding 2)-4), 8), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further regarding 2), Wabl et al cannot teach away from using AID in their invention: Wabl et al do not teach AID. Applicants attempt to use passages in Wabl et al, directed to knowledge in the art regarding somatic hypermutation at the time Wabl et al was filed, to argue that Wabl et al teaches away from using AID. This specious reasoning does not take into account that the involvement of AID in hypermutation or class switching was not appreciated at the time Wabl et al was filed: that is why Muramatsu et al is used in this rejection.

Further regarding 3), the passage relied upon by applicants is taken out of context. It is background material supplied by Wabl et al to characterize the knowledge in the art at the time of filing regarding ways to stop hypermutation after the desired mutation has occurred (see the proceeding ¶). It does not teach anything in the way of why it would be undesirable to add a mutator gene to a hybridoma itself in order to make a mutator cell line. The teachings of Wabl et al are missing the fact that AID is the cornerstone of class switching and hypermutation, a fact complemented by the teachings of Muramatsu et al. Thus, transfection of the AID gene into the cells and methods of Wabl et al as the "cellular factor" effecting hypermutation (column 8, lines

14-20) is the crux of the combination of Wabl et al and Muramatsu et al. To perform such a transfection in literally any cell line of B or pre B cell lineage (e.g. a hybridoma) is thus taught by Wabl et al in combination with Muramatsu et al.

Regarding 5), the vector map supplied teaches nothing about the placement of the IRES-EGFP in the vector of Muramatsu et al, who merely used this segment of the Clontech vector (see page 561, first column, last ¶ of Muramatsu et al). Furthermore, see the explanation of 5' sequences in a plasmid set forth above.

Regarding 6), the passages referred to by applicants in the US 2005/0095712 publication do not teach the criticality of these mRNA levels. At best they indicate the level of expression of the gene to be mutated is relevant and perhaps not dependent on specific cis-acting sequences in the target gene. Because an Ig gene is mutated in a non-B cell when AID is expressed does not necessarily mean that hypermutation is dependent upon a high rate of transcription, nor does the fact that strong expression of the AID in non-B and B cells results in mutation. The results of Muramatsu et al in transfecting a cell with AID and inducing class switching indicates that mRNA levels of the desired gene (Ig heavy chain in this instance) were sufficient, i.e., Fig. 1.

Regarding 7) it is not clear, and applicants do not explain, where the Examiner has questioned the truth telling of applicants.

Regarding 8), 9) and 10), applicants are referred to the title of Muramatsu et al "Class Switch Recombination and Hypermutation Require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme"; the abstract; page 554, first column, third ¶; and page 561, first column, second full ¶, which states (emphasis added):

"Although we have provided the evidence that AID is the essential component for both CSR and hypermutation, their molecular mechanisms still remain to be solved."

The above passages do not resemble speculation, they are conclusions backed up by rather convincing experiments, in contrast to applicants assertions and opinions regarding the teachings of Muramatsu et al. Furthermore, the mechanism by which AID exerts its effects does not appear to be relevant. The mechanistic steps by which AID works are not steps performed by the skilled artisan, but rather a complex chemical reaction performed by the cell itself. It is enough to know that AID itself is a crucial component of the CSR and hypermutation pathways, there is no requirement that it act directly to mediate hypermutation as long as it is clear it is an essential component of the pathway (i.e. the results of Muramatsu et al). Papavasiliou et al do not teach that the role of AID in hypermutation is unclear, as applicants assert: what they actually say is "..the function of AID in somatic hypermutation is far from clear..". There is a significant difference: the role of AID in hypermutation is established, the exact mechanism by which it exerts its effects, i.e. it function, may not be clear, but that argument is not germane to this rejection.

Further regarding 9), in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., stable, inherited changes at the DNA level) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further regarding 10), applicants present no reasoning or evidence as to why AID would not lead to stable changes in the DNA of a cell, even if it is involved in RNA editing. The final result of the pathway of which AID seems to be a crucial component is just such a stable, inherited change. The skilled artisan does not need to know the exact mechanism by which AID exerts its effects to be useful in the methods of Wabl et al, it is enough to know through the results of Muramatsu et al that AID is a crucial, necessary component in the CSR and hypermutation pathway. A review of the articles cited by applicants reveals no teachings that AID would not be useful in the claimed methods, rather, they reinforce the teachings of Muramatsu et al, that AID is a requirement for both the CSR and hypermutation pathways.

Claims 5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (5,885,827, of record) and in view of Muramatsu et al (2000, of record) as applied to claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 above, further in view of in view of Wang et al (US Patent Publication 2003/0119190, of record). **This rejection is maintained for reasons made of record in the Office Action dated 9/13/2007, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 2/12/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Wang et al does not overcome the deficiencies of Wabl and Muramatsu et al. Because Wabl and Muramatsu et al are deemed to not have any deficiencies for reason set forth above, this assertion is unconvincing.

Claims 273, 274, and 275 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US 5,885,827, of record) and Muramatsu et al (Cell, 2000, of record) as applied to claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 above, and further in view of Griffiths (US 5,885,827, of record). **This rejection is maintained for reasons made of record in the Office Action dated 9/13/2007, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 2/12/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Griffiths et al does not overcome the deficiencies of Wabl and Muramatsu et al. Because Wabl and Muramatsu et al are deemed to not have any deficiencies for reason set forth above, this assertion is unconvincing.

Claims 18, 285 and 286 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US 5,885,827, of record) and Muramatsu et al (Cell, 2000, of record) as applied to claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 above, and further in view of Hondo et al (US Patent 6,815,194, of record). **This rejection is maintained for reasons made of record in the Office Action dated 9/13/2007, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 2/12/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Hondo et al does not overcome the deficiencies of Wabl and Muramatsu et al because it is directed to methods of expressing and preparing a

recombinant AID protein. Because Wabl and Muramatsu et al are deemed to not have any deficiencies for reason set forth above, this assertion is unconvincing.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See PEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633